Australian Government

Medical Services Advisory Committee

Public Summary Document

Application No. 1600 – Genetic testing for heritable kidney disease (other than Alport syndrome)

Applicant: Professor Judith Savige

Date of MSAC consideration: MSAC 82nd Meeting, 29-30 July 2021
MSAC 81st Meeting, 31 March – 1 April 2021

Context for decision: MSAC makes its advice in accordance with its Terms of Reference, visit the MSAC website

1. Purpose of application

An application requesting MBS listing of genetic testing for heritable kidney disease (other than Alport syndrome) was received from Professor Judith Savige by the Department of Health. PASC recommended this application follow the clinical utility card (CUC) format, which is designed for use in MSAC applications related to genetic testing for germline variants.

After this application had been supported by MSAC, correspondence from KidGen was received by the Department proposing revisions to the fee and/or descriptors for items AAAA1 and AAAA2.

2. MSAC's advice to the Minister

March-April 2021 MSAC consideration
After considering the strength of the available evidence in relation to comparative safety, clinical effectiveness and cost-effectiveness, MSAC supported the creation of Medicare Benefits Schedule (MBS) items for genetic testing for heritable kidney disease other than Alport syndrome in affected individuals, cascade testing in biological relatives, testing to enable reproductive decision making (for recessively inherited variants: cascade testing for reproductive partners and potentially affected fetuses), and data reanalysis. MSAC accepted that there is a clinical need for this testing, and considered that this testing has clear value for first-degree relatives and reproductive planning. The cost-effectiveness is likely to be similar to that of comparable genetic tests, and there is a relatively low financial impact to the MBS and low risk of leakage. MSAC requested that the Department revise the item descriptor structure and wording, remove the requirement for consultation with a clinical geneticist, and revise the proposed fees in line with existing items. MSAC foreshadowed a future move towards genericised MBS items for cascade testing in biological relatives, cascade reproductive genetic testing, and data re-analysis.

Draft item descriptors are provided in section 6 of this document, though MSAC noted that they require restructuring and revision.

July 2021 MSAC consideration

After considering the strength of the available evidence in relation to comparative safety, clinical effectiveness and cost-effectiveness, MSAC did not support increasing its previously advised fee for items "AAAA1" and "AAAA2" for genetic testing for inheritable kidney disease other than Alport syndrome, advising that the previously supported fee for the Medicare Benefits Schedule (MBS) item 73358 was appropriate for these tests. MSAC advised that the item descriptors for both these items should be amended to be for "whole exome or whole genome sequencing", based on the appropriateness of the two test methods for this genetic testing, the current lack of universal access to whole genome sequencing, and consistency with existing MBS items.

Consumer summary

Professor Judith Savige applied for public funding via the Medicare Benefits Schedule (MBS) for genetic testing for certain kidney diseases. These problems can lead to decreased kidney function over time, worsening until the person develops kidney failure and needs dialysis or a kidney transplant to stay alive. There are already MBS items for testing for the kidney disease Alport syndrome – this application proposed testing for other kidney diseases that can be inherited.

Genetic testing involves taking a blood sample from people who are likely to have heritable kidney disease and sending it to a laboratory to test whether they have genetic variants associated with kidney disease. If someone is found to have a genetic variant associated with kidney disease, their first-degree relatives (parents, children, brothers and sisters) may also be recommended to get tested, even if they do not have symptoms. This is called cascade testing. Cascade testing allows people to make more informed health and family planning decisions. This will help their relatives to be diagnosed earlier so they can start treatment to delay disease progression. If a family member does not have a mutation, they do not have to have regular long-term monitoring for the disease. Cascade testing would also allow avoiding transplanting a kidney from a relative who turns out to also have kidney disease.

People whose genetic makeup includes particular gene variants, and who are planning to have children, will be advised to consider testing for the same variant for their reproductive partner too. The need for this testing depends on the type of gene and how it is inherited.

New genes are often being discovered, and may be added in the future to the group of genes tested. Pathology laboratories can sequence the patient's whole genome (all of a person's genetic makeup), and reanalyse the same data later as new genes are identified.

MSAC acknowledged that there is a clinical need for this genetic testing, as it is already a standard part of care in many places. Having this genetic testing on the MBS helps to ensure equity of access to testing for everyone.

MSAC supported the application, but noted some issues with the fees and the way the MBS items are worded remain to be resolved.

MSAC's recommendation to the Commonwealth Health Minister

MSAC recommended that genetic testing of heritable kidney diseases other than Alport syndrome be listed on the MBS. MSAC noted there was a clinical need for this testing, and considered it to be safe and effective, has clear value to consumers, is probably good value for money, and is not expected to cost a lot to the MBS. MSAC also noted the benefits of this testing for helping people make reproductive decisions. MSAC asked the Department to make some changes to the wording and the fees before listing these tests on the MBS.

3.   Summary of consideration and rationale for MSAC's advice

March-April 2021 MSAC consideration
MSAC noted the application requested MBS items for genetic testing for heritable kidney disease other than Alport syndrome in affected individuals, cascade testing in biological relatives, and cascade testing to enable reproductive decision-making.

MSAC noted the five proposed populations and their associated proposed tests:
- Population 1 (age agnostic): Whole-genome sequencing (WGS) for germline gene variants in ≥1 genes causative for heritable autosomal dominant polycystic kidney disease (ADPKD) – fee $2,400

- Population 2 (children): WGS for germline gene variants in ≥1 genes causative for heritable chronic kidney disease in children aged under 18 – fee $2,400

- Population 3: Genetic testing in first-degree relatives of index cases for familial germline gene variants identified in ≥1 genes causative for heritable kidney disease – fee $400

- Population 4: Genetic testing in reproductive partners, for reproductive decision making – fee $500

- Population 5: Genetic testing for determining familial variant(s) in a fetus – fee $500.

MSAC noted that genetic testing for heritable kidney diseases was currently widespread clinical practice and part of standard of care, and that this was noted in the applicant's pre-MSAC response. This application thus addresses equity of access.

MSAC considered that genetic testing provides certainty of diagnosis and additional prognostic information, which may lead to change in therapy to avoid early onset renal failure and help guide the management of extra-renal complications. Genetic testing also helps to avoid renal biopsies and non-beneficial interventions. For relatives who test negative for the familial variant, testing may obviate the need for unnecessary clinical appointments and investigative tests and disease monitoring. MSAC also noted that testing would enable the avoidance of inadvertent renal transplants from affected relatives. Finally, MSAC accepted that genetic testing provides information to families to inform reproductive decision making.

MSAC accepted that the clinical claims are plausible and probable, but noted the uncertainty that remains after evaluating the limited clinical trial data, due to the high risk of bias in trials looking at analytical validity, diagnostic yield, clinical validity, prognosis and predictive

validity. MSAC noted that no evidence was identified to ascertain clinical utility and therapeutic effectiveness. The overall diagnostic yield was identified to be at least 20%, which MSAC considered acceptable.

MSAC considered the proposed fees to be high, and recommended altering the fees in line with comparable existing and supported MBS items, such as a fee of $500 for the data reanalysis item.

MSAC considered that the MBS item descriptor should be agnostic with respect to test methodology, as laboratories may choose to perform WGS, whole-exome sequencing, or conventional gene panels.

MSAC noted that the descriptor wording for item AAAA2 should be agnostic with respect to age, and it advised that this is appropriate because, for example, adults with "childhood-type" non-cystic kidney diseases should still be eligible for testing if the disease manifested in adulthood. MSAC noted that although populations 1 and 2 were split for the economic evaluation, it was not necessary to retain this split for two MBS items. MSAC advised the Department to consider the wording in the item descriptors for heritable cardiomyopathies (Application 1599) when finalising the descriptors for these items. MSAC also supported an MBS item for reproductive decision-making, noting that this would be appropriate where a recessively inherited variant has been identified in the proband, and that the test should sequence the whole gene in the reproductive partner. MSAC considered that merging these new MBS items with the items for Alport syndrome to be problematic, and recommended that they stay separate. MSAC revised the fee for reproductive partner testing item DDDD from $500 to $1200, noting that while this is higher than the fee for the existing cystic fibrosis reproductive partner testing item (MBS item 73349), $1,200 was appropriate due to the greater complexity of single gene sequencing required here compared to that for the cystic fibrosis gene, *CFTR*.

MSAC recommended removing the requirement for consultation with a clinical geneticist, as the patient consent process helps to manage this. MSAC noted the importance of the involvement of multidisciplinary teams.

MSAC noted the complex economic evaluation was largely uninformative for decision-making as MSAC considered the estimate of 'cost per informed reproductive decision' to be highly uncertain and difficult to interpret, given that it relies on assumptions about patient behaviour and the population risk for each disease varies. MSAC considered the 'cost per measure of diagnostic yield', estimated to be approximately $3,243 per identified variant for population 1 (all ages) and $19,200 for population 2 (children; assuming a weighted average distribution of the defined disease subtypes). MSAC accepted that these estimates were cost-effective compared with either the cost per identified pathogenic gene variant or chromosomal aberration as described in other previously supported genetic testing applications. MSAC considered the total financial impact to the MBS to be relatively small ($3.33–$3.50 million per year), based on test fees of $2,400 and $400, though noted some uncertainty remained around the expected utilisation, which should be reviewed once implemented.

MSAC noted possible cost offsets from avoiding a proportion of ultrasound monitoring in patients who test negative.

MSAC considered the KidGen data to be highly valuable, as extensive genetic testing has already been done in Australia as part of this research. MSAC noted that diagnostic yield improves when a multidisciplinary team (MDT) is involved in the patient's care[1,2], and KidGen has established 19 MDTs around Australia.

July 2021 MSAC consideration

MSAC noted this discussion related to application 1600 – Genetic testing for heritable kidney disease (other than Alport syndrome). MSAC recalled it had supported MBS funding for this testing at its 81st meeting in March/April 2021. MSAC recalled that both supported item descriptors were for whole genome sequencing (WGS) and analysis at a fee of $2100. MSAC noted the correspondence from KidGen, which proposed that the supported fee of $2100 was too low and would lead to out-of-pocket costs for patients. KidGen proposed two options:

1. Maintain the wording of AAAA1 and AAAA2 as being "whole genome sequencing" but raise the fee from $2100 to $2400; or
2. Maintain the wording of AAAA1 as being "whole genome sequencing" but raise the fee from $2100 to $2400, and amend the wording of AAAA2 to be "whole exome or genome sequencing" and preserve the fee as $2100.

MSAC noted that the greatest permissible gap is currently $84.70.

MSAC noted that a fee of $2400 would not be consistent with the most similar MBS item, 73358, for whole exome or genome sequencing and analysis with a fee of $2100. MSAC also noted that costs at the VCGS laboratories used by KidGen are often significantly higher than testing costs at other public pathology laboratories. MSAC advised that a fee increase was therefore not appropriate.

MSAC considered that allowing laboratories to perform WES would not result in an inferior analysis compared to WGS for these disorders. MSAC noted that very few laboratories are accredited to perform WGS currently, and so considered that also supporting whole exome sequencing (WES) will increase patients' equity of access.

MSAC advised the descriptors should be altered to permit either WGS or WES for both items AAAA1 and AAAA2, and retain the $2100 fee for both. MSAC considered that this change would allow accredited testing to be done by more laboratories, increasing equitable access while still providing an appropriate test.

4.   Background

This is the first submission for genetic testing for heritable kidney disease other than Alport syndrome. It was considered by PASC in December 2019 and April 2020.

A related application is previous MSAC Application 1449 – genetic testing for Alport syndrome, which was supported by MSAC in March 2018 on the basis of acceptable clinical safety and effectiveness and low risk of leakage. MSAC considered that genetic diagnoses

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[1] Groopman EE, et al. (2019). Diagnostic utility of exome sequencing for kidney disease. *N Engl J Med*, 380: 142–151.
[2] Jayasinghe, K, et al. (2021). Clinical impact of genomic testing in patients with suspected monogenic kidney disease. *Genet Med* 23: 183–191.

would reduce the number of renal biopsies and provide prognostic information[3]. This recommendation was implemented as two MBS items listed on 1 May 2019: MBS item 73298 for the sequencing of genetic variants in *COL4A3, COL4A4* and *COL4A5* for the diagnosis of Alport syndrome, and MBS item 73299 for family member cascade testing in the same three genes.

5. Prerequisites to implementation of any funding advice

Pathology laboratories must participate in an External Quality Assurance Program (EQAP) and obtain National Association of Testing Authorities (NATA) accreditation to offer MBS-funded genetic testing services in Australia. The National Pathology Accreditation Advisory Council (NPAAC) stated that an EQAP is available through RCPA QAP Pty Ltd. The RCPA QAP stated that it is considering a proposal to develop an EQA for NGS panel testing for kidney diseases. Existing EQAs are available for autosomal dominant polycystic kidney disease (ADPKD) targeting only the *PKD1* and *PKD2* genes, not for whole genome sequencing as in this application.

NPAAC also noted that this testing is already established in a public sector laboratory in Australia.

6. Proposal for public funding

The DCAR proposed two MBS items for affected individual testing: in patients with cystic kidney disease (population 1; Table 1) and in children aged under 18 years with chronic kidney disease other than cystic kidney disease or Alport syndrome (population 2; Table 2). The DCAR also proposed MBS items for data re-analysis (Table 3), and cascade testing (population 3; Table 4).

MSAC advised that the fees for these items should be align with the fees for comparable existing items. MSAC noted that the descriptor for item EEEE would only cover fetal testing based on the parents' genotypes, and advised that item descriptor AAAA will therefore have to be altered during implantation from that shown below, to encompass fetal testing based on indications such as ultrasound indicating a renal abnormality such as those seen in fetuses with CAKUT.

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[3] MSAC Public Summary Document (PSD) for application 1449

Table 1   Proposed item descriptor, genetic testing for the purpose of diagnosis (testing of the affected individual)

Category 6 – PATHOLOGY SERVICES Group P7 – GENETICS
Item AAAA1

Characterisation, by whole genome sequencing and analysis, of germline variants in one or more of the genes implicated in heritable cystic kidney disease, if:
 	
    (a)   The characterisation is:
 	
        (i) requested by a consultant physician practising as a clinical geneticist; or
        (ii) requested by a consultant physician practising as a specialist nephrologist, *following consultation with a clinical geneticist*; and
 	
    (b)   The patient has a renal abnormality and is strongly suspected of having a monogenic condition.
 	
Applicable once per lifetime.

Fee: **$2,400.00** *$2,100.00*   Benefit: 75% = **$1,800.00** *$1,575.00*   85% = **$2,040.00** *$1,785.00*

Source: DCAR Table 1, with changes made by the Department and MSAC (in italics)

Table 2   Proposed item descriptor, genetic testing for the purpose of diagnosis (testing of the affected individual)

Category 6 – PATHOLOGY SERVICES Group P7 – GENETICS
Item AAAA2

Characterisation, by whole genome sequencing and analysis, of germline variants in one or more of the genes implicated in heritable kidney disease, if:
 	
    (a)   The characterisation is:
 	
        (i) requested by a consultant physician practising as a clinical geneticist; or
        (ii) requested by a consultant physician practising as a specialist nephrologist, *following consultation with a clinical geneticist*; and
 	
    (b)   The patient *has is aged under 18 years with* chronic kidney disease (other than cystic disease or Alport syndrome) and is strongly suspected of having a monogenic condition.
 	
Applicable once per lifetime.

Fee: **$2,400.00** *$2,100.00*   Benefit: 75% = **$1,800.00** *$1,575.00*   85% = **$2,040.00** *$1,785.00*

Source: DCAR Table 2, with changes made by the Department and MSAC (in italics)

In the pre-ESC response, the applicant stated that funding testing in children but not adults for the same disease would create inequity. All causes of heritable kidney disease that present in childhood may also present for the first time in adults[4]. Sometimes the diagnosis is overlooked in childhood, but more often this is adult-onset disease. Genetic diagnoses made in childhood are usually autosomal recessive variants, whereas those made in adulthood are more likely to be autosomal dominant variants.

In the pre-ESC response, the applicant raised concerns about the proposed testing methodology being WGS, when WES is used more often and cheaper. The applicant stated that WES detects 90-95% of genetic variants, and that WGS is only needed for patients suspected to have ADPKD. In the ratified PICO, PASC had earlier noted that the test-agnostic approach could potentially result in suboptimal testing in certain patient groups. PASC advised that a targeted panel / WES is inadequate for patients with ADPKD, and they represent the largest patient subgroup. Based on feedback from KidGen following the April

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[4] Savige, J., Ratnaike, S., & Colville, D. 2011. Retinal Abnormalities Characteristic of Inherited Renal Disease. *JASN*, **22**(8): 1403-1415.

2020 PASC meeting, PASC stated that the appropriate test methodology for populations 1 and 2 is WGS. The rejoinder responded that the number of studies assessing WGS alone was small, though technological advances mean the cost of WGS is reducing, and adoption of WGS technologies offers increasing efficiency.

In the pre-ESC response, the applicant stated that the only laboratory currently performing WGS is Royal Children's Hospital/Victorian Clinical Genetics Service/Murdoch Children's Research institute in Melbourne. The rejoinder responded that a search of the NATA website[5] on 27 January 2021 indicated two additional laboratories in Melbourne (Australian Genome Research Facility and Peter Doherty Institute) and two laboratories in Sydney (Garvan Institute and NSW Health Pathology). There are 15 sites across Australia accredited to perform WES or NGS. In the pre-MSAC response, the applicant stated that genetic testing for heritable kidney disease is widely available in Europe.

Table 3   Proposed item descriptor, data re-interrogation (testing of the affected individual)

	Category 6 – PATHOLOGY SERVICES Group P7 – GENETICS
Item BBBB	
Re-analysis of genetic data obtained under item AAAA1 or AAAA2, for characterisation of previously unreported germline gene variants related to the clinical phenotype, as requested by a consultant physician practising as a clinical geneticist or a consultant physician practising as a specialist paediatrician, *following consultation with a clinical geneticist*, for a patient with a strong clinical suspicion of a monogenic condition. Performed no more than twice per patient. Performed at an interval of not less than 18 months following AAAA1 or AAAA2. If repeated, must be at an interval of not less than 18 months from previous BBBB	
Fee: **$576.00** *$500.00* Benefit: 75% = **$432.00** *$375.00* 85% = **$489.60** *$425.00*	

Source: DCAR, Table 3, with changes made by MSAC (in italics)

Table 4   Proposed item descriptor, cascade testing of first degree relatives

	Category 6 – PATHOLOGY SERVICES Group P7 – GENETICS
Item CCCC	
Request by a clinical geneticist, or requested by a specialist or consultant physician providing professional genetic counselling services, for detection of a single gene variant in a first degree relative of a patient with a known monogenic cause of kidney disease where previous genetic testing under item AAAA1, AAAA2, or BBBB has identified the causative variant. *Applicable once per variant per lifetime.*	
Fee: **$400.00** Benefit: 75% = **$300.00** 85% = **$340.00**	

Source: DCAR Table 4, with additions made by the Department (in italics)

The DCAR noted that although PASC raised the question of reproductive partner testing for recessive conditions, no MBS item was proposed for reproductive partner testing in the ratified PICO. It was therefore not included in the DCAR. In the pre-ESC response, the applicant commented that patients' major reason for genetic testing is to have children who do not inherit the disease. In general they use PGT prior to IVF, for which the genetic variant needs to be known.

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[5] https://www.nata.com.au/accredited-facility [accessed 27 Jan 2021]

At the Department's request, MBS items for reproductive partner testing (population 4; Table 5) and fetal testing (population 5; Table 6) were added in the rejoinder.

Table 5   Proposed descriptor, genetic testing for the purpose of reproductive decision making

	Category 6 – PATHOLOGY SERVICES Group P7 – GENETICS
Item DDDD	

Detection of variants of a single gene known to cause heritable kidney disease for the purpose of reproductive decision making, if:
  (a) The detection is:
     (i) requested by a consultant physician practising as a clinical geneticist; or
     (ii) requested by a consultant physician practising as a specialist nephrologist, *following consultation with a clinical geneticist*; and
  (b) The patient:
     (i) is the reproductive partner of an individual known to be a carrier of pathogenic variant/s causative of heritable kidney disease that has a recessive mode of inheritance; and
     (ii) a service to which item AAAA1, AAAA2, BBBB or CCCC applies has identified the causative gene for the patient's reproductive partner
  (c) The test methodology has:
     (i) sufficient diagnostic range and sensitivity to detect at least 95% of pathogenic variant/s likely to be present in the patient.	

Fee: *$500.00* *$1200.00*	
Benefit: 75% = *$375.00* *$900.00* 85% = *$425.00* *$1020.00*	

Source: Rejoinder Table R1, with changes made by MSAC (in italics).

Table 6   Proposed descriptor, genetic testing for the purpose of determining variant/s in a fetus where one or both parents are carriers

	Category 6 – PATHOLOGY SERVICES Group P7 – GENETICS
Item EEEE	

Testing of a pregnant patient, where one or both prospective parents are known to be affected by or carriers of known pathogenic variant/s causative of heritable kidney disease, for the purpose of determining whether monogenic variants are present in the fetus, if:
  (a) The detection is:
     (i) requested by a consultant physician practising as a clinical geneticist; or
     (ii) requested by a consultant physician practising as a specialist nephrologist*, following consultation with a clinical geneticist*; and
  (b) The fetus is at 25% or more risk of inheriting a monogenic variant known to cause kidney disease.	

Fee: **$400.00**	
Benefit: 75% = **$300.00** 85% = **$340.00**	

Source: Rejoinder Table R2, with changes made by MSAC (in italics).

MSAC revised the fee for reproductive partner testing item DDDD from $500 to $1200, noting that while this is higher than the fee for the existing cystic fibrosis reproductive partner testing item (MBS item 73349), $1,200 was appropriate due to the greater complexity of single gene sequencing required here compared to that for the cystic fibrosis gene, *CFTR*.

The Department also suggested the addition of the following practice note to the descriptors for items AAAA1, AAAA2, and CCCC:

*PN.0.23 Prior to ordering these tests the ordering practitioner should ensure the patient (or approximate proxy) has given informed consent. Testing should only be performed after genetic counselling. Appropriate genetic counselling should be provided to the patient either by the specialist treating practitioner, a genetic counselling service or a clinical geneticist on referral. Further counselling may be necessary upon receipt of the test results.

7. Summary of public consultation feedback/consumer Issues

Public consultation feedback and/or consumer comments were received from seven individuals, one renal healthcare professional organisation, and one patient advocacy organisation. Targeted consultation feedback was received from two genomics organisations and one individual (research clinician). Consumer feedback highlighted the burden of living with heritable kidney disease.

Overall, consultation feedback strongly supported public funding for genetic testing for heritable kidney disorders. The main benefits of funding the proposed service are:

- Equitable access to testing by all consumers – at present provision of testing is highly variable across Australia and largely dependent on which tests are able to be funded in particular states/territories or services.
- Sustainable funding leading to ongoing access to testing.
- More certainty in diagnosis and prognosis.
- Potentially providing a diagnosis in people with atypical presentation, and permitting a diagnosis before adulthood in patients with ADPKD. Shortening the diagnostic odyssey.
- Earlier access to treatment.
- Better guided clinical management. May reduce the use of expensive, risky and invasive diagnostic investigations such as renal biopsy.
- Receiving a negative result from cascade testing provide great relief, for example to individuals from families with many affected members, who grow up fearing kidney disease may descend on them as they get older.
- Value of knowing: consumers with kidney disease described feeling that having this disease gave them no control over their lives. A genetic diagnosis would provide knowledge and empowerment to assist affected people in their lifestyle choices.
- Avoiding monitoring in genotype negative family members.
- Informing family planning decisions, including publicly funded pre-implantation genetic diagnosis where this is required. Consumer comments noted wanting to start a family but without passing the disease they suffer from on to future generations.
- Enabling the identification of appropriate living kidney donors for transplantation.

The potential disadvantages of funding the proposed testing would be:

- No disadvantage – doing genetic testing will not leave the patient worse off, because even if no genetic diagnosis is made they would still receive care as their clinical presentation indicated.
- Families may not wish to know the outcomes of genetic tests or be offered tests.
- The family risks would be the same for this test as for genetic tests for any other condition.
- Potential impacts on income protection insurance.

- Uncertainty over who owns patients' genetic data, and who can access it – access by insurers would need to be prevented.

One patient advocacy organisation conducted a member survey to assess support for MSAC application 1600, and found strong support for MBS funding this genetic testing. This included support for genetic testing for family planning purposes, with 82% of patient respondents and 89% of family member respondents saying they would use genetic testing for family planning.

Consumers and organisations also made other points about technical aspects of this application in consultation. Main points were:

- There was very strong and widespread support for genetic counselling being provided prior to testing.
  - If a nephrologist was not comfortable in delivering genetic testing and results follow-up, then referral to a clinical geneticist should occur – therefore it would be important for clinical geneticists to also be able to order tests for affected individuals.
  - One genomics organisation already provides genomics education for renal clinicians, ensuring clinicians would be knowledgeable on when to test and what to do with the results.
- The MBS item should be technology agnostic but include exome sequencing at minimum, so that analysis can be expanded if no genetic diagnosis is found in the initial virtual panel. Using a static panel would preclude further investigation.
- Genome sequencing is the required testing method for ADPKD, which makes up approximately half the caseload for adult renal genetics clinics, due to the challenges of multiple pseudogenes.
- The term "inherited" kidney disease (as originally proposed by the applicant) may be inappropriate as some genetic kidney disease is caused by *de novo* variants.
- It may be possible to increase diagnostic yield through multidisciplinary team review. The diagnostic yield of genomic sequencing in an unselected cohort of patients was just under 10%[6], yet utilising patient review by a multidisciplinary team (nephrologist, geneticist and genetic counsellor) to pragmatically select the cohort for testing raised the diagnostic yield to 39%[7]. This multidisciplinary clinic model was also preferred by patients, according to a survey of 221 patients. Genomic testing could be restricted to clinicians in a multidisciplinary clinic, rather than based on disease phenotypes.

8. Proposed intervention's place in clinical management

Description of Proposed Intervention
The PICO Advisory Sub-Committee (PASC) advised that the appropriate intervention was whole genome sequencing (WGS), to be used in addition to current investigative tests in affected individuals. Cascade testing, in first degree relatives of index patients, is proposed to

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[6] Groopman EE, et al. (2019). Diagnostic utility of exome sequencing for kidney disease. *N Engl J Med*, 380: 142–151.
[7] Jayasinghe, K, et al. (2021). Clinical impact of genomic testing in patients with suspected monogenic kidney disease. *Genet Med* 23: 183–191.

be agnostic with respect to testing methodology. The Department-contracted assessment report (DCAR) additionally proposed an MBS item for subsequent data re-interrogation.

Description of Medical Condition(s)
The DCAR stated that chronic kidney disease is defined as abnormalities of kidney structure or function, present for more than three months, with implications for health[8]. There are five stages of kidney disease: the early stages (1 and 2) are usually asymptomatic, the middle stages (3 and 4) are often symptomatic from the primary kidney disease (but can have secondary signs and symptoms) as kidney function slows and the amount of urea and creatinine in the blood increases, and end stage kidney disease (ESKD, stage 5) where a patient requires dialysis or a kidney transplant to stay alive[9].

Approximately 30% of chronic kidney disease can currently be attributed to a heritable monogenic cause, where a single gene variant is known to be causal[10]. Three modes of inheritance are recognised: X-linked dominant, autosomal recessive and autosomal dominant. The incidence of *de novo* variants (which occur after fertilisation) varies by disease type, and will have an impact on the extent of cascade testing required. The *de novo* variant rate is approximately 10%, which means that parents and siblings are not affected, but offspring of the affected individual may be, depending on the anticipated mode of inheritance.

PASC advised that the seven populations initially proposed by the applicant (including one cascade testing population) could be simplified to two populations of patients with chronic kidney disease plus a cascade testing population, and for completeness the Department requested the addition of reproductive partner and fetal testing populations:

- Population 1: Patients with autosomal dominant polycystic kidney disease (ADPKD)
- Population 2: Children aged under 18 years with chronic kidney disease (excluding Alport syndrome and cystic disease). Comprising four subpopulations:
    - Congenital anomalies of the kidney and urinary tract (CAKUT)
    - Glomerular diseases
    - Complement diseases
    - Tubular diseases
- Population 3: First degree relatives of index cases in populations 1 and 2
- Population 4: Reproductive partners of probands with recessively inherited variants
- Population 5: Fetal testing population

The distribution of patients eligible for WGS as part of population 2 within the four major disease sub-types was based on Australian data provided by KidGen.

Clinical management algorithm
Genetic testing is proposed to be conducted in addition to existing testing. The current (Figure 1) and proposed (Figure 2) clinical management algorithms for cystic kidney disease represent populations 1 and 3 in the DCAR's analysis. The current (Figure 3) and proposed (Figure 4) clinical management algorithms for children aged under 18 years with chronic

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[8] KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. 2013, Kidney Inter Suppl, Vol. 3, pp. 1-150.
[9] Australian Institute of Health and Welfare. Chronic Kidney Disease. Canberra: Australian Government, 2019.
[10] Personalized medicine in chronic kidney disease by detection of monogenic mutations. Connaughton, Dervla M and Hildebrandt, Friedhelm. 2019, Nephrol Dial Transplant, pp. 1-8.

kidney disease excluding Alport syndrome and cystic disease represent populations 2 and 3 in the DCAR's analysis.
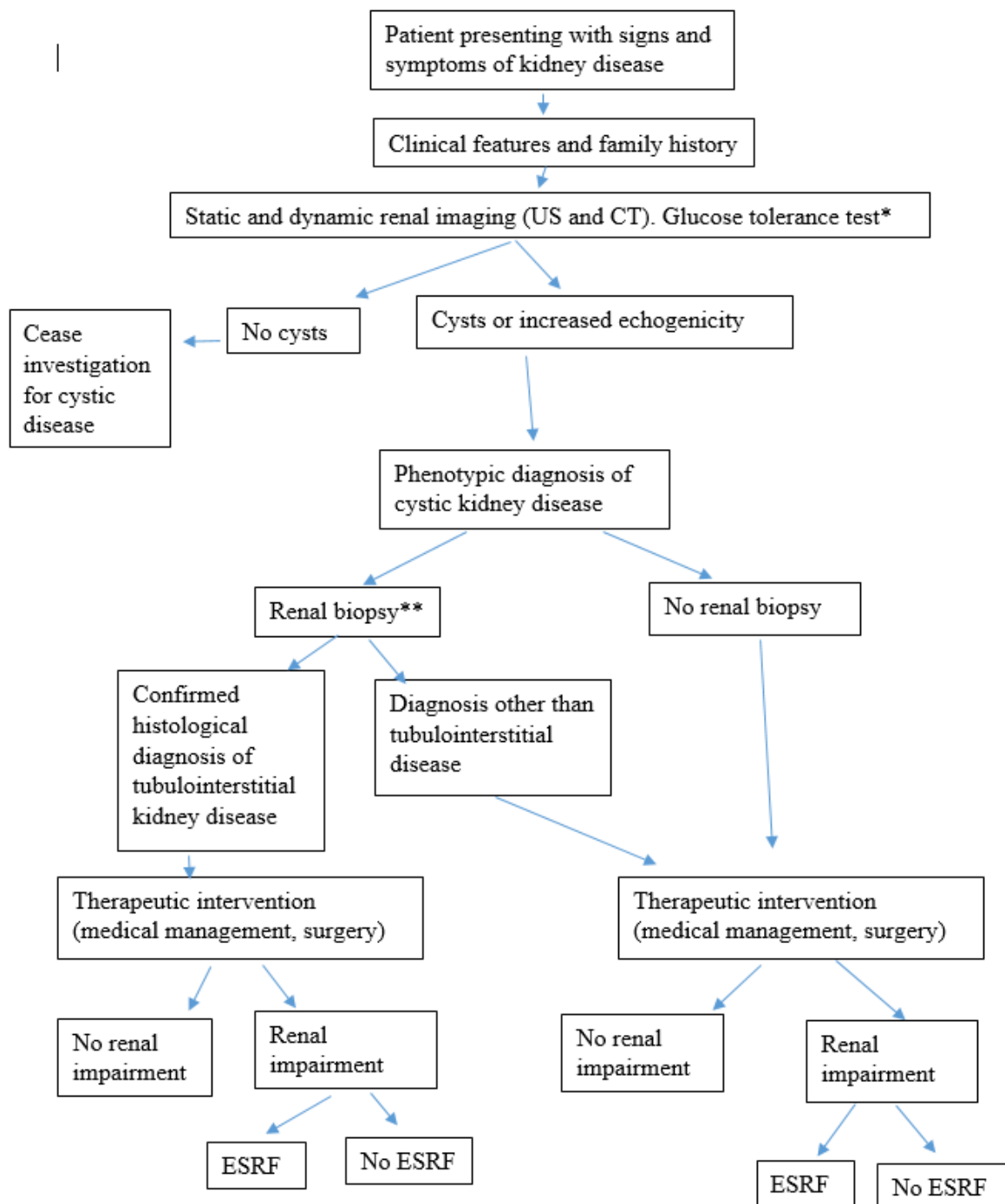
Figure 1 Current clinical management algorithm for cystic kidney disease

The term ESRF is used here to describe end stage kidney disease (ESKD)

Abbreviations: CT = computed tomography; ESRF = End Stage Renal Failure; US = ultrasound

Notes: * an oral glucose tolerance test for diabetes may be conducted to detect diabetes caused by *HNF1B* related disease; ** Renal biopsy is only required for definitive diagnosis of autosomal dominant tubulointerstitial kidney disease (including MCKD and *HNF1B-related* disease)

Source: DCAR Figure 1, from Ratified PICO Figure 2.
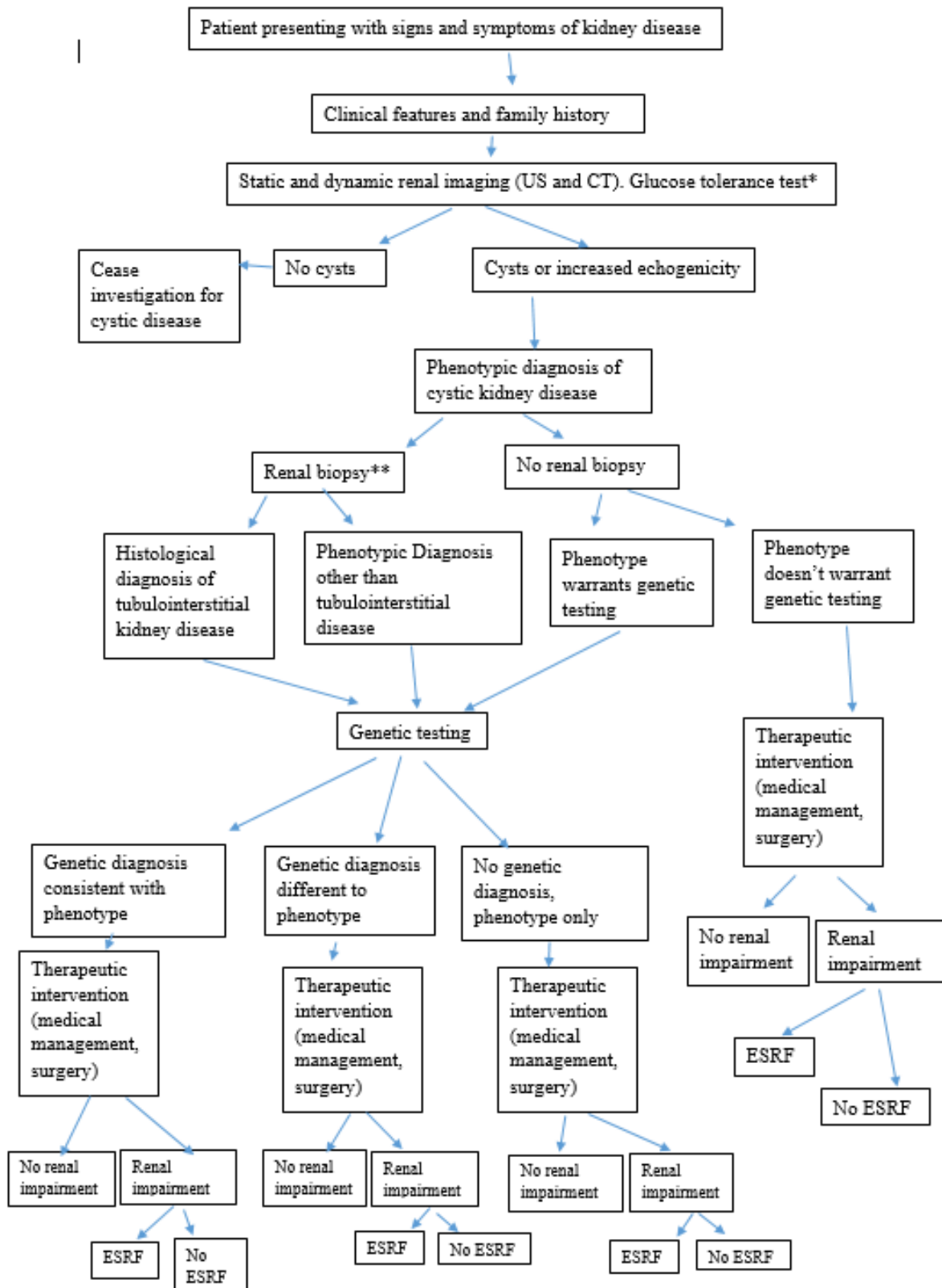
Figure 2 Proposed clinical management algorithm for cystic kidney disease

The term ESRF is used here to describe end stage kidney disease (ESKD)

Abbreviations: CT = computed tomography; ESRF = End Stage Renal Failure; US = ultrasound

Notes: * an oral glucose tolerance test for diabetes may be conducted to detect diabetes caused by *HNF1B* related disease; ** Renal biopsy is only required for definitive diagnosis of autosomal dominant tubulointerstitial kidney disease (including MCKD and *HNF1B*-related disease) Source: DCAR Figure 2, from Ratified PICO Figure 3.

Figure 3 Current clinical management algorithm for chronic kidney (renal) disease in children aged under 18 years (excluding Alport syndrome & cystic disease)
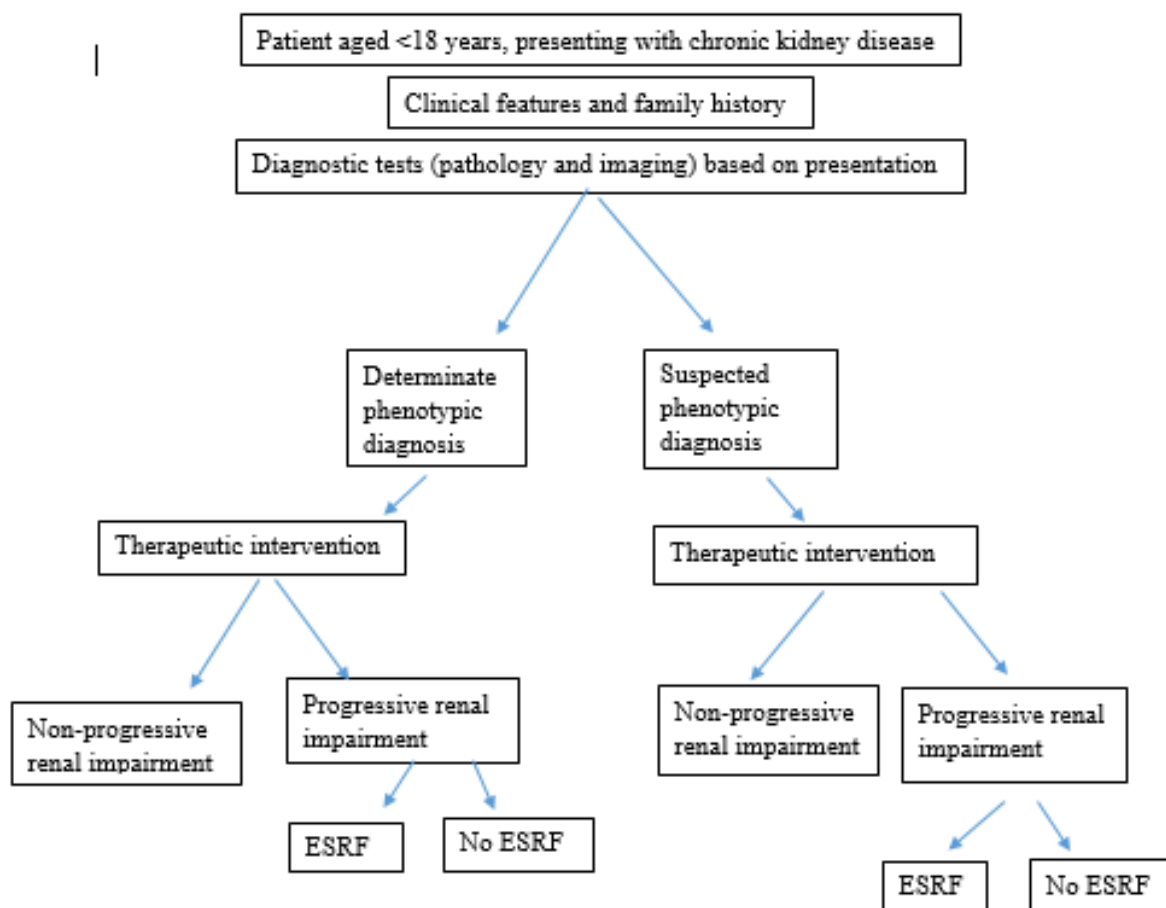
The term ESRF is used here to describe end stage kidney disease (ESKD)
Abbreviations: ESRF = End Stage Renal Failure
Source: DCAR Figure 3, from Ratified PICO Figure 4.

```
                  ┌─────────────────────────────────────────────────┐
                  │ Patient aged <18 years, presenting with chronic  │
                  │                kidney disease                    │
                  └─────────────────────────────────────────────────┘
                                       │
                  ┌─────────────────────────────────────────┐
                  │     Clinical features and family history │
                  └─────────────────────────────────────────┘
                                       │
             ┌──────────────────────────────────────────────────┐
             │ Diagnostic tests (pathology and imaging) based on │
             │                  presentation                     │
             └──────────────────────────────────────────────────┘
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Figure 4 flow chart:

- Patient aged <18 years, presenting with chronic kidney disease
  - Clinical features and family history
    - Diagnostic tests (pathology and imaging) based on presentation
      - Determinate phenotypic diagnosis
        - Genetic testing not warranted
          - Therapeutic intervention
            - Non-progressive renal impairment
            - Progressive renal impairment
              - ESRF
              - No ESR
        - Genetic testing warranted → Genetic testing
      - Indeterminate phenotypic diagnosis → Genetic testing
        - Genetic testing
          - Genetic diagnosis confirms phenotypic diagnosis
            - Therapeutic intervention
              - Non-progressive renal impairment
              - Progressive renal impairment
                - ESRF
                - No ESRF
          - Genetic diagnosis differed to phenotypic diagnosis
            - Therapeutic intervention
              - Non-progressive renal impairment
              - Progressive renal impairment
                - ESRF
                - No ESRF
          - No genetic diagnosis, phenotypic diagnosis
            - Therapeutic intervention
              - Non-progressive renal impairment
              - Progressive renal impairment
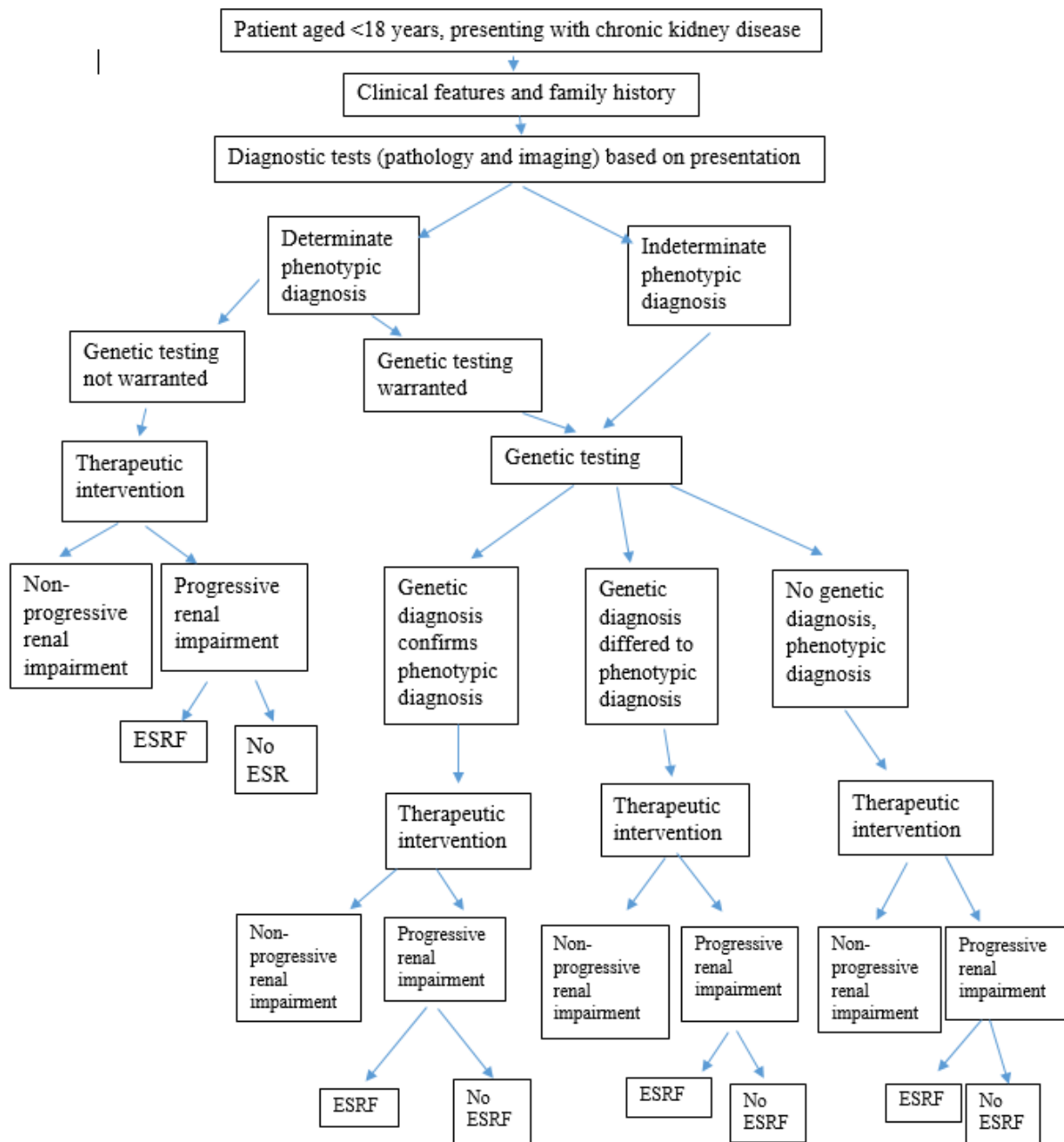   - ESRF
                - No ESRF

Figure 4 Proposed clinical management algorithm for chronic kidney (renal) disease in children aged under 18 years (excluding Alport syndrome & cystic disease)

The term ESRF is used here to describe end stage kidney disease (ESKD)
Abbreviations: ESKD = End Stage Renal Failure.
Source: DCAR Figure 4, from Ratified PICO Figure 5.

The DCAR stated that the addition of genetic testing in the clinical management algorithm for affected individuals is simple and may reduce the time taken to reach a definitive diagnosis and commence optimal medical therapy. This would increase health care resource utilisation in the short term, which may be partially offset by reduced renal biopsy, repeat imaging, and pathology tests associated with the 'diagnostic odyssey'. A timely diagnosis and initiation of optimal medical therapy should delay the onset of renal failure and the costs associated with end stage kidney disease.

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Once a definitive diagnosis is made for the affected individual through genetic testing (populations 1 and 2), their first-degree relatives may also be screened for the disease (cascade testing, population 3). A positive test result enables earlier monitoring and treatment of currently asymptomatic individuals and ensures that disease carriers do not act as kidney donors for the index patient. A negative test result removes the need for monitoring in 'at risk' individuals. Targeted genetic and reproductive counselling can be provided, including prenatal diagnosis, *in vitro* fertilization (IVF) and pre-implantation genetic diagnosis.

9.   Comparator

The DCAR stated that the agreed comparator is 'no genetic testing for heritable kidney disease', with diagnosis reliant on clinical criteria and (non-genetic) laboratory investigations, and previous medical and family history. PASC advised that non-genetic laboratory investigations could include diagnostic imaging.

Genetic testing is intended to be used as an adjunct diagnostic tool to clinical examination, family history, diagnostic pathology, and renal imaging. If heritable kidney disease is suspected but cannot be categorically determined phenotypically, the affected individual would be referred for genetic testing.

10.   Comparative safety

The DCAR stated that genetic testing is only indicated for patients who cannot be definitively diagnosed phenotypically. It is possible for harm to be caused by genetic testing through genetic misdiagnosis, missed diagnosis, or incidental findings. It is possible for harm to be caused by the comparator, 'no genetic testing', through adverse events associated with inappropriate therapeutic interventions.

11.   Comparative effectiveness

Clinical claim
The clinical claim is that, relative to no genetic testing, WGS-based genetic testing for heritable kidney disease other than Alport syndrome shows superior safety and effectiveness in terms of disease diagnosis and change in clinical management of patients.

Characteristics of the evidence base
Due to the lack of direct clinical trial evidence, a linked evidence approach was adopted for all three populations. The quality of the included evidence was low. No randomised clinical trials or large-scale prospective longitudinal studies could be retrieved. The study design was mostly retrospective with an inherently high risk of bias (Table 7).

Table 7   Key features of the included linked evidence

Type of evidence	Description	Number	Risk of bias
Analytical validity	*Analytical sensitivity and specificity*	*Population 2.3, k=4 , n=81* *Population 2.4, k=5 , n=680* *Population 3, k=6 , n=89*	*High*
Diagnostic yield	*Diagnostic yield (proportion of variant positive cases)*	*Population 1, k=16 , n=1534* *Population 2.1, k=17 , n=2342* *Population 2.2, k=17 , n=4528* *Population 3, k=6 , n=475*	*High*
Clinical validity	*Genotype prediction of phenotype*	*No evidence*	-
Prognosis	-Disease progression -Renal transplantation -Prenatal screening -Preimplantation genetic testing	Population 1, k=1 , n=146	*High*
Predictive validity	*Treatment effect modification by genetic variant status*	Population 1, k=4 , n=18 Population 2.1, k=2 , n=193 Population 2.2, k=7 , n=1126 Population 2.3, k=4 , n=312 Population 2.4, k=3 , n=146	*High*
Clinical utility	*Impact on clinical management*	*No evidence (limited evidence for Sanger sequencing in population 1 – renal treatment and pre-implant testing; indirect limited evidence for NGS in population 2.1 - termination)*	-
Therapeutic effectiveness	*Response to therapies*	*No evidence*	-

k = number of studies; n = total sample size; NGS = next generation sequencing.
Source: DCAR Table 5, with changes made by ESC (in italics).

Analytical validity

The DCAR stated that complete information about analytical accuracy was not available for complement and tubular diseases subpopulations, and for ADPKD, CAKUT and glomerular diseases the number of studies was small (Table 8).

Table 8   Summary statistics for accuracy of WGS against Sanger sequencing (reference standard)

Accuracy	Population 1, ADPKD (k=1)	Population 2			
		CAKUT (k=1)	Glomerular diseases (k=2)	Complement diseases (k=2)	Tubular diseases (k=1)
Sensitivity, % (95% CI)	99.2 (96.8, 99.9)	100 (98.6, 100)	95.6 (94.3, 96.6)	-	100
Specificity, % (95% CI)	99.9 (99.7, 100.0)	99.71 (99.27, 99.92)	99.7 (99.5, 99.9)	-	
Positive predictive value, % (95% CI)	100	98.4 (96.0, 99.4)	99.3 (98.6, 99.6)	100	100
Negative predictive value, % (95% CI)	99.9% (99.6, 100)	100	98.2 (97.7, 98.6)	-	

ADPKD = autosomal dominant polycystic kidney disease; CAKUT = congenital anomalies of the kidney and urinary tract; CI = confidence interval; k = number of studies.
Source: DCAR, Table 6

Diagnostic yield

The DCAR stated that diagnostic yield was the main effectiveness outcome used for assessing the diagnostic performance of WGS-mediated genetic testing (Table 9). The diagnostic yield of WGS/NGS varied considerably by disease subtype, and a high degree of inter-study heterogeneity (I^2) was observed in diagnostic yield meta-analyses in all study populations. Multiple factors could have led to this result, including differences in study design and settings, variant detection and interpretation methods, and genetic and clinical heterogeneity, among other factors.

Table 9   Summary of results on the diagnostic performance of genetic testing and cascade testing

	Diagnostic yield (pooled estimate, random-effects) % (95% CI) I^2, *p*-value, *df*	
	Affected individual testing (Populations 1 and 2)	**Cascade testing (Population 3)**
Population 1 autosomal dominant polycystic kidney disease (ADPKD)		
Overall DY	79 (75, 83) 78%, *p*=0.00, *df*=15	56 (43, 70) 0%, *p*=0.45, *df*=2
Exemplars' DY	74 (69, 80) 85%, *p*=0.00, *df*=15	NA
Population 2 CKD in children aged under 18 years (excluding Alport syndrome and cystic disease)		
Subpopulation – congenital anomalies of kidney and urinary tract (CAKUT)		
Overall DY	17 (12, 21) 90%, *p*=0.00, *df*=16	NA
Exemplars' DY	2 (1, 3) 59%, *p*=0.00, *df*=14	NA
Subpopulation – glomerular diseases		
Overall DY	29 (25, 33) 82%, *p*=0.00, *df*=16	70 (35,93)
Exemplars' DY	16 (12, 21) 90%, *p*=0.00, *df*=14	60 (26,88)
Subpopulation – complement diseases		
Overall DY	40 (11, 70) 88%, *p*=0.00, *df*=4	NA
Exemplars' DY	21 (8, 34) 39%, *p*=0.17, *df*=3	NA
Subpopulation – tubular diseases		
Overall DY	58 (40, 77) 95%, *p*=0.00, *df*=4	88 (70, 98)
Exemplars' DY	14 (8, 20) 63%, *p*=0.07, *df*=2	NA

CI = confidence interval; df = degrees of freedom; DY = diagnostic yield; NA = not applicable; CKD = chronic kidney disease.
Source: DCAR, Table 7

Prognosis

ESC noted that evidence for change in management was in the form of prognostic evidence, rather than direct evidence that diagnosis changed clinical management (i.e., clinical utility) (Table 10). The DCAR stated that the results for population 2-glomerular diseases show that immunosuppressive therapies fail to prevent the progression to ESKD in patients with genetically determined steroid-resistant nephrotic syndrome (SRNS). Death rate was found to be higher in atypical haemolytic uraemic syndrome (aHUS) (population 2-complement diseases subgroup) patients with genetic variants compared with the non-genetic group. As this result was derived from a single retrospective study, its significance is not clear. Large scale randomised prospective studies are required to show that timely genetic diagnosis has the potential to identify patients at increased risk of death.

Table 10 Key prognosis findings for the linked evidence comparison of genetic testing, relative to no genetic testing, in chronic kidney disease patients

Outcomes, number of studies, study references	Participants	Quality of evidence (GRADE) [a]	Genetic diagnosis % (n/N) [95%CI]	No genetic diagnosis % (n/N) [95% CI]	Fischer exact test for the difference between non-genetic and genetic disease	Comments
Death rate, k=1 [11]	**Population 2:** Complement diseases aHUS patients with genetic versus non-genetic diagnosis	⊕⊕⊙⊙	33% (26/79) [23, 44]	6% (4/67) [2, 15]	p=0.0001	Death was more frequent in aHUS patients with genetic variants compared with the non-genetic group.

aHUS = atypical haemolytic uraemic syndrome; CI = confidence interval; k = number of studies; n = number of positives; N = total sample size.

[a] GRADE Working Group grades of evidence:[12]

⊕⊕⊕⊕ **High quality:** We are very confident that the true effect lies close to that of the estimate of effect.

⊕⊕⊕⊙ **Moderate quality:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

⊕⊕⊙⊙ **Low quality:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.

⊕⊙⊙⊙ **Very low quality:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

Source: based on DCAR, Table 8

Predictive validity

ESC noted that the evidence for health benefit from change in management was in the form of clinical prediction of therapeutic effectiveness by genetic test result (Table 11). The DCAR stated that in population 1, the systematic literature search retrieved one suitable study investigating the treatment effects before and after tolvaptan therapy in patients with ADPKD with and without genetic variations. Although significant improvement in the reduction of total kidney volume and estimated glomerular filtration rate was observed in patients with ADPKD with *PKD1/2* variants compared to patients without *PKD1/2* variants after tolvaptan treatment, the study design was retrospective and non-randomised and the sample size was small (n=18). Therefore, conclusive evidence was not available.

The DCAR noted that in population 2-glomerular diseases subtype, results pooled from four studies showed that patients with genetic variants do not respond to immunosuppressive therapies (mainly cyclosporin). Therefore, the evidence indicates that unnecessary exposure to immunosuppressive agents and their side-effects can be avoided in SRNS patients with genetic disease. For population 2-complement diseases, results obtained from two studies indicated that the variant status of patients did not influence response to eculizumab treatment.

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[11] Noris M, et al. 2010, 'Relative role of genetic complement abnormalities in sporadic and familial aHUS and their impact on clinical phenotype', *Clin J Am Soc Nephrol*, 5(10): 1844-59.

[12] Guyatt, G., et al. (2013). GRADE guidelines: 11. Making an overall rating of confidence in effect estimates for a single outcome and for all outcomes. *J Clin Epidemiol,* 66(2): 151-157.

Table 11 Summary of key predictive validity findings for the linked evidence comparison of chronic kidney disease patients with versus without genetic variants

Outcomes, number of studies, study references	Participants	Quality of evidence (GRADE) a	Genetic variant % (n/N) [95% CI]	No genetic variant % (n/N) [95% CI]	Fischer exact test for the difference (treatment effect modification)	Comments
Improvement in kidney function after tolvaptan therapy, k=1 [13]	**Population 1**: ADPKD patients before and after tolvaptan therapy	⊕⊕⊙⊙	28%	-37%	p=0.01	*ΔeGFR/y b improved more with tolvaptan therapy in the group with a variant in PKD1 or PKD2 than in the group without a variant in one of these genes*
Annual rate of TKV increase (%ΔTKV/y) c [14]			-6.7%	-1.1%	p=0.02	*Less reduction of total kidney volume was observed in ADPKD patients with PKD1/2 variants as compared to patients with no PKD1/2 variants after tolvaptan treatment*
Patients progressing to ESKD, k=6 [15,16,17,18,19,20]	**Population 2** Glomerular diseases SRNS patients with genetic versus non-genetic diagnosis	⊕⊕⊕⊙	63% (108/172) [52, 76]	24% (88/360) [19, 30]	p=0.0000	*Lower rate of progression to ESKD on immunosuppressive therapies in SRNS patients without a genetic variant, compared to those with a variant*
Complete response to immuno-suppressive	**Population 2**: Glomerular diseases SRNS patients with genetic versus non-genetic diagnosis	⊕⊕⊕⊙	2% (3/128) [0.5, 6.8)	32% (203/635) [28, 37]	p=0.0000	*Higher complete response to immunosuppressive agents in SRNS patients without genetic variants compared to those with a variant*

[13] Sekine A, et al. 2020, 'Genetics May Predict Effectiveness of Tolvaptan in Autosomal Dominant Polycystic Kidney Disease', *Am J Nephrol*, 51(9): 745-51.

[14] Sekine A, et al. 2020, 'Genetics May Predict Effectiveness of Tolvaptan in Autosomal Dominant Polycystic Kidney Disease', *Am J Nephrol*, 51(9): 745-51.

[15] Bezdíčka M, et al. 2018, 'Genetic diagnosis of steroid-resistant nephrotic syndrome in a longitudinal collection of Czech and Slovak patients: a high proportion of causative variants in *NUP93'*, *Pediatr Nephrol*, 33(8): 1347-63.

[16] Bierzynska A, et al. 2017, 'Genomic and clinical profiling of a national nephrotic syndrome cohort advocates a precision medicine approach to disease management', *Kidney Int*, 91(4): 937-47.

[17] Büscher AK, et al. 2016, 'Rapid response to cyclosporin A and favorable renal outcome in nongenetic versus genetic steroid–resistant nephrotic syndrome', *Clin J Am Soc Nephrol*, 11(2): 245-53.

[18] Kari JA, et al. 2013, 'Steroid-resistant nephrotic syndrome: impact of genetic testing', *Ann Saudi Med*, vol. 33, no. 6, pp. 533-8.

[19] Giglio S, et al. 2015, 'Heterogeneous genetic alterations in sporadic nephrotic syndrome associate with resistance to immunosuppression', *J Am Soc Nephrol*, 26(1): 230-6.

[20] McCarthy HJ, et al. 2013, 'Simultaneous sequencing of 24 genes associated with steroid-resistant nephrotic syndrome', *Clin J Am Soc Nephrol*, 8(4): 637-48.

Outcomes, number of studies, study references	Participants	Quality of evidence (GRADE) [a]	Genetic variant % (n/N) [95% CI]	No genetic variant % (n/N) [95% CI]	Fischer exact test for the difference (treatment effect modification)	Comments
therapies, k=4 [21,22,23,24]						
Complete TMA response to eculizumab treatment, k=2 [25,26]	**Population 2**: Complement diseases Response of aHUS paediatric patients to tolvaptan therapy	⊕⊕⊕⊙	76% (13/17) [50, 93]	74% (14/19) [49, 91]	p= 1.000	Variant status of patients does not greatly influence response to eculizumab treatment

k = number of studies; CI = confidence interval; n = number of positives; N = total sample size; ESKD = end-stage renal disease; SRNS = steroid resistant nephrotic syndrome; aHUS = atypical haemolytic uraemic syndrome; ADPKD=autosomal dominant polycystic kidney disease; ΔeGFR= change in estimated glomerular filtration rate; TKV= change in total kidney volume; TMA=thrombotic angiopathy.
[a] GRADE Working Group grades of evidence:[27]
⊕⊕⊕⊕ **High quality:** We are very confident that the true effect lies close to that of the estimate of effect.
⊕⊕⊕⊙ **Moderate quality:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
⊕⊕⊙⊙ **Low quality:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
⊕⊙⊙⊙ **Very low quality:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.
[b] Improvement of ΔeGFR/y = (ΔeGFR/y after tolvaptan) − (ΔeGFR/y before tolvaptan). Source: Figure 2 of the study.
[c] The rate at which a kidney enlarges in a patient with ADPKD depends on the number of cysts, the rates at which individual cysts expand, and the effects of intrinsic and extrinsic growth factors — TKV (the sum volume of the two kidneys) is a composite indicator of all of these variables, and is associated with a reduction in renal function.
Source: based on DCAR Table 8, with changes made by ESC (in italics)

In the pre-ESC response, the applicant stated that genetic testing of cystic kidney disease patients allows prediction (based on genetic variants) of which individuals have more severe disease, will develop early onset kidney failure and need aggressive treatment including tolvaptan. In the rejoinder, the assessment group responded that they agree that early diagnosis can slow the rate of renal disease progression, however, no evidence linking the time of diagnosis, the provision of early care, and improved clinical outcomes was identified in the literature, so none was modelled.

The applicant also stated in the pre-ESC response that precipitants of aHUS include oral contraceptives and pregnancy, so having this diagnosis allows the person to be prepared and

[21] Bezdíčka M, et al. 2018, 'Genetic diagnosis of steroid-resistant nephrotic syndrome in a longitudinal collection of Czech and Slovak patients: a high proportion of causative variants in *NUP93'*, *Pediatr Nephrol*, 33(8): 1347-63.
[22] Bierzynska A, et al. 2017, 'Genomic and clinical profiling of a national nephrotic syndrome cohort advocates a precision medicine approach to disease management', *Kidney Int*, 91(4): 937-47.
[23] Kari JA, et al. 2013, 'Steroid-resistant nephrotic syndrome: impact of genetic testing', *Ann Saudi Med*, 33(6): 533-8.
[24] Trautmann A, et al. 2017, 'Long-term outcome of steroid-resistant nephrotic syndrome in children', *J Am Soc Nephrol*, 28(10): 3055-65.
[25] Greenbaum LA, et al. 2016, 'Eculizumab is a safe and effective treatment in pediatric patients with atypical hemolytic uremic syndrome', *Kidney Int*, 89(3): 701-11.
[26] Kumar G, et al. 2019, 'Eculizumab in paediatric atypical haemolytic uraemic syndrome: Lessons learned from a single-centre experience in the United Arab Emirates', *J Paediatr Child Health*, 55(10): 1237-40.
[27] Guyatt, G., et al. (2013). GRADE guidelines: 11. Making an overall rating of confidence in effect estimates for a single outcome and for all outcomes. *J Clin Epidemiol,* 66(2), 151-157.

monitored. A diagnosis of aHUS is also useful to know as people with aHUS have retinal disease and may go blind[28].

The applicant stated in the pre-ESC response that further value is derived from genetic testing due to early detection of renal impairment in family members, which in the broader community is usually not suspected. These people can then receive generic treatment such as angiotensin converting enzyme (ACE) inhibitors to slow their rate of renal failure progression.

Potential clinical utility

The DCAR's systematic review for the impact of genetic testing on the clinical management of patients in population 1 – cystic kidney disease, identified four relevant studies.

The natural history of ADPKD includes the progression to ESKD in a large proportion of patients. Consequently, many patients with ADPKD are candidates for renal transplantation. Since deceased donor organs are in short supply, living related donation could be considered if ADPKD can be excluded in the prospective donor. Genetic testing has been recommended in the potential living related kidney donations (LRKD) if the donor is below 40 years of age, as imaging studies may be insufficient to rule out the future possibility of ADPKD in asymptomatic donors[29]. No studies were identified evaluating the role of WGS in renal transplantation, however, two studies investigating the pre-transplant genetic evaluation using Sanger sequencing were found (Table 12).

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[28] Savige J, et al. 2016. 'Retinal disease in the C3 glomerulopathies and the risk of impaired vision'. *Ophthalmic Genet*. **37**(4): 369-376.
[29] Simms RJ, et al. 2015, 'Genetic testing in the assessment of living related kidney donors at risk of autosomal dominant polycystic kidney disease', *Transplantation*, 99(5): 1023-9.

Table 12 Genetic testing results for living related kidney donors

Study, N	Intervention, Genes	Variant positive	Variant negative	Gene variant/s	Imaging-based renal transplantation outcome, n/N	GT-based renal transplantation outcome, n/N
Huang 2009 [30], 4 living related kidney donors	Sanger sequencing *PKD1*, *PKD2*	100% (4/4)	-	*PKD1* (4/4) *PKD2* (1/4)	-No abnormalities detected, -Proceed with donation, 50% (2/4)	-No parental disease-causing variant detected -Proceed with donation, 50% (2/4)
					-Abnormalities detected -Preclude RTx -Don't proceed with donation, 25% (1/4)	-No parental disease-causing variant detected -Proceed with donation, 25% (1/4)
					-Abnormalities detected -Preclude RTx -Don't proceed with donation, 25% (1/4)	-GT inconclusive -Don't proceed with donation, 25% (1/4)
Simms 2015 [31], 25 living related kidney donors	Sanger sequencing *PKD1*, *PKD2*	4% (1/25)	96% (24/25)	*PKD1*	-Abnormalities detected -Preclude RTx -Don't proceed with donation, 1 (4%)	-Pathogenic variant detected -Precluded RTx -Don't proceed with donation, 4% (1/25)
					-Abnormalities detected -Preclude RTx -Don't proceed with donation, 4% (1/25)	-No known variant detected -Proceed with donation, 4% (1/25)
					-Imaging inconclusive -GT recommended	-No known variant detected -Proceed with donation, 12% (3/25)

GT = genetic testing; RTx = renal transplantation.
Source: DCAR, Table 41.

The DCAR stated that pre-implantation genetic testing (PGT) has been used in families at risk for ADPKD to select and implant healthy embryos created by *in vitro* fertilization (IVF). Patients with ADPKD planning a family are recommended to receive genetic counselling and PGT before pregnancy[32]. However, no consensus exists on the mandatory use of such testing. Patients and/or parents are suggested to make the final decision. Supportive evidence for PGT using WGS was not found. However, representative PGT studies using Sanger sequencing to detect *PKD1* and *PKD2* variants in population 1 are summarised below (Table 13).

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[30] Huang E, et al. (2009). DNA testing for live kidney donors at risk for autosomal dominant polycystic kidney disease. *Transplantation*, 87(1): 133.

[31] Simms RJ, et al. (2015). Genetic testing in the assessment of living related kidney donors at risk of autosomal dominant polycystic kidney disease. *Transplantation*, 99(5): 1023-9.

[32] Chapman AB, et al. 2015, 'Autosomal-dominant polycystic kidney disease (ADPKD): executive summary from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference', *Kidney Int*, 88(1): 17-27.

Table 13 Studies assessing the role of PGT in patients with ADPKD

Study	Gene/s	Country	GT intervention	Couples counselled (N)	Couples with at least one PGT cycle, n (%)	Unaffected live births from PGT, n (%)	Unaffected live births in couples without PGT, n (%)
Snoek 2020 [33]	*PKD1* (n=35) *PKD2* (n=2)	Netherlands	NR	98 (out of which 37 were ADPKD)	43 (44)	24 (56)	15 (41) *
Berckmoes 2019 [34]	*PKD1* (n=33) *PKD2* (n=2)	Belgium	Multiplex PCR	65	45 [†]	26 (58)	NR

PGT = preimplantation genetic testing; NR = not reported; GT = genetic testing; PCR = polymerase chain reaction.
* 37 couples did not undergo PGT, 15/37= 41%. [†] Source: Table III of the study.
Source: DCAR, Table 42.

The DCAR also found two studies investigating the prenatal diagnostic utility of WES in population 2 – CAKUT subpopulation (Table 14).

Table 14 Key results of the included studies for genetic testing in population 2 - CAKUT subpopulation (impact on clinical management)

Study	N	Diagnostic yield % (n/N)	Pregnancy outcome in patients with genetic variant	Pregnancy outcome in patients without genetic variant	Study limitations
Lei 2017 [35]	30 fetuses (all fetuses were diagnosed with echogenic kidneys by ultrasound examination)	20 (6/30)	Live Birth: 33.3% (2/6) Termination: 66.7% (4/6)	Live Birth: 50% (12/24) Termination: 38% (9/24) None: 13% (3/24)	-Prospective long-term follow-up information was missing. - Study did not evaluate whether genetic testing results influenced patients' decision to terminate pregnancy
Lei 2020 [36]	163 fetuses (all fetuses were diagnosed with echogenic kidneys by ultrasound examination)	12 (20/163)	Live Birth: 30% (6/20) Termination: 65% (13*/20)	Live Birth: 59% (93/158[†]) Termination: 29.1% (46/158)	Long-term prognosis remains unknown as the age of the oldest patient at follow-up was only 5 years -Study did not evaluate whether genetic testing results influenced patients' decision to terminate pregnancy

* One patient was lost to follow up.
[†] Pregnancy outcomes were not available for five patients
Source: DCAR, Table 53.

[33] Snoek R, et al. 2020, 'Preimplantation Genetic Testing for Monogenic Kidney Disease', *Clin J Am Soc Nephrol*, 15(9): 1279-86.
[34] Berckmoes V, et al. 2019, 'Factors influencing the clinical outcome of preimplantation genetic testing for polycystic kidney disease', *Hum Reprod*, 34(5): 949-58.
[35] Lei TY, et al. (2017). Whole-exome sequencing for prenatal diagnosis of fetuses with congenital anomalies of the kidney and urinary tract. *Nephrology Dialysis Transplantation*, 32(10): 1665-75.
[36] Lei TY, et al. (2020). Whole-exome sequencing in the evaluation of fetal congenital anomalies of the kidney and urinary tract detected by ultrasonography. *Prenatal Diagnosis*, 40(10): 1290-9.

Translation issues

The DCAR identified seven applicability issues, two extrapolation issues, and one transformation issue (Table 15). These issues were addressed in pre-modelling studies.

Table 15 Summary of translation issues, pre-modelling studies, and their use in the economic evaluation

Issue	Pre-modelling study and use in economic evaluation	Results used in sensitivity analysis
Applicability issues		
Exemplar genes and diagnostic yield for economic evaluation in population 2	Meta-analysis identified *HNF1B* and *PAX2* as exemplar genes for CAKUT, with a combined diagnostic yield of 2%.	95% CI used in sensitivity analysis
	Meta-analysis identified *NPHS1* and *NPHS2* as exemplar genes for glomerular diseases, with a combined diagnostic yield of 16%	95% CI used in sensitivity analysis
	Meta-analysis Identified *CFH* as exemplar gene for complement disorder, with a diagnostic yield of 21%.	95% CI used in sensitivity analysis
	Meta-analysis identified *SLC12A3* as exemplar gene for tubular diseases, with a diagnostic yield of 14%.	95% CI used in sensitivity analysis
Evidence of therapeutic effectiveness for population 2-CAKUT	Literature review to identify treatments for CAKUT. Screening, monitoring and medicines identified in the review are applied as interventions in the economic model.	None
Baseline age and eGFR for populations 1, 2 & 3	Section B informed baseline estimates of age and eGFR for populations 1, 2 & 3.	95% CI used in PSA
Estimating annual eGFR decline for populations 1, 2 & 3	Section B informed CKD progression. Literature review informed estimate of eGFR decline for the general population.	95% CI used in PSA
Estimating event rates in ESKD	ANZDATA informed ESKD event rates and outcomes	None
Modelling changes to reproductive decision making	Literature review informed impact of genetic diagnosis on reproductive decision making. Uptake of PGD and prenatal diagnosis is an economic model input	None
Estimating health care resource use in Australia	Literature review informed resource use relevant to Australia. Costs of treatment estimated in AU$	None
Extrapolation issues		
Extrapolating treatment effect to the model time horizon	Glomerular diseases (SRNS): Assumed 'complete response' to treatment was maintained for patient's lifetime.	N/A
	Complement disorders (aHUS): Assumed 'complete TMA response' was maintained for patient's lifetime.	Time horizon truncated to 1 year
Transformation issues		
Identifying utilities for use in the economic evaluation	Literature review informed utility value inputs	95% CI used in sensitivity analysis

aHUS = atypical haemolytic uraemic syndrome; ANZDATA = Australia and New Zealand Dialysis & Transplant Registry; CAKUT = congenital abnormalities of the kidney and urinary tract; CI = confidence interval; CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; ESKD = end stage kidney disease; PGD = pre-implantation genetic diagnosis; PSA = probabilistic sensitivity analysis; SD = standard deviation; SRNS = steroid-resistant nephrotic syndrome; TMA = thrombotic microangiography.
Source: DCAR, Table 9.

12.   Economic evaluation

Cost-effectiveness and cost-utility analyses were presented for both analyses (populations 1 & 3, and populations 2 and 3) (Table 16).

Table 16 Summary of the economic evaluation

Perspective	Healthcare system
Comparator	No genetic testing, standard care treatment
Type of economic evaluation	Cost-effectiveness and cost-utility analysis
Sources of evidence	Systematic review
Time horizon	50 years in the model base case
Outcomes	QALYs and informed reproductive decisions
Methods used to generate results	Decision tree and Markov models, CKD progression modelled by eGFR decline, ESKD transitions modelled by transition probabilities
Health states in Markov model	Normal kidney function, CKD Stage, CKD Stage 2, CKD Stage 3a, CKD Stage 3b, CKD Stage 4, ESKD on dialysis, ESKD after transplant, untreated ESKD, and dead
Cycle length	1 year
Discount rate	5% for both costs and outcomes (QALYs)
Software packages used	TreeAge Pro Healthcare 2020

CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; ESKD = end stage kidney disease; QALYs = quality adjusted life years
Source: DCAR, Tables 10 and 14.

The DCAR stated that the economic model consisted of a decision tree reflecting the results of genetic testing in populations 1 and 3 and subsequent reproductive decisions. Lifetime costs and outcomes for populations 1 and 3 were captured through Markov models attached to the decision tree. Reproductive decisions were recorded within the decision tree. The Markov model for population 1 was a CKD model, where disease progression was modelled by estimated glomerular filtration rate (eGFR) decline observed in a clinical trial. For population 2, affected individuals who experience a complete response to treatment entered the population risk model, where disease progression was modelled by eGFR decline based on age and comorbidities. The Markov model for population 3 was a population risk model, where disease progression was modelled by GFR decline based on age and comorbidities of the Australian general population.

Populations 1 and 3
The overall costs and outcomes (QALYs), and incremental costs and outcomes as calculated for the testing strategy and comparative testing strategy in the model, and using the base case assumptions, are shown in Table 17. The total costs for the intervention (genetic testing) were higher than the comparator costs (no genetic testing) for populations 1 and 3. The incremental cost of genetic testing was partially offset by the avoided costs of unnecessary monitoring in first degree relatives. Since it was assumed that WGS does not change the clinical management of individuals with ADPKD, there were no QALYs gained.

Table 17 Incremental cost-effectiveness ratio of genetic testing versus no testing – populations 1 & 3

	Cost	Incremental cost	Effectiveness (QALYs)	Incremental effectiveness (QALYs)	ICER
Affected individuals (population 1)					
Index test and associated interventions	$86,139	$2,436	11.11	0.00	Undefined
Comparator	$83,703		11.11		
Affected individuals + cascade testing (populations 1 and 3)					
Index test and associated interventions	$285,623	$3,409	64.78	0.00	Undefined
Comparator	$282,214		64.78		

ICER = incremental cost-effectiveness ratio; QALY = quality adjusted life year
Source: DCAR Table 11, as revised in the rejoinder.

The overall costs and outcomes in terms of the number of informed reproductive decisions, and associated ICER, are shown in Table 18. When only reproductive decision making is considered, each genetic test of an affected individual plus associated cascade testing results in 2.24 informed reproductive decisions made by affected individuals and their first degree relatives. This translates to an ICER of $3,351 per informed reproductive decision.

Table 18 Incremental cost-effectiveness ratio of genetic testing versus no testing – informed reproductive decisions for populations 1 & 3

	Cost	Incremental cost	Effectiveness (informed reproductive decision)	Incremental effectiveness (informed reproductive decision)	ICER ($/informed reproductive decision)
Cost per informed reproductive decision made (populations 1 and 3)					
Index test and associated interventions	$326,578	$7,500	2.24	2.24	$3,351
Comparator	$319,078		0.00		

ICER = incremental cost-effectiveness ratio
Source: DCAR Table 12, as revised in the rejoinder.

Key drivers of the economic model for populations 1 and 3 are presented in Table 19.

Table 19 Key drivers of the economic model for populations 1 & 3

Description	Method/Value	Impact
No discounting of reproductive decisions	The model registers all reproductive decisions in the first model cycle, so no discounting is applied. Discounting future reproductive decisions would increase the ICER. The size of the impact is uncertain.	Uncertain, favours intervention
Diagnostic yield of *PKD1/2*	The model used the mean diagnostic yield for exemplar genes.	Low, uncertain
Costs of ADPKD monitoring in first degree relatives	The costs of monitoring for ADPKD were applied to all first degree relatives in the 'NO TEST' scenario but only relatives who test positive in the 'TEST' scenario	Low, favours intervention

ADPKD = autosomal dominant polycystic kidney disease; CI = confidence interval.
Source: DCAR, Table 13

Populations 2 and 3

The overall costs and outcomes (QALYs), and incremental costs and outcomes as calculated for the testing strategy and comparative testing strategy in the model, while using the base case assumptions, are shown in Table 20. For the population 2-glomerular diseases sub-

population, the clinical evidence highlights the therapeutic futility of treating patients with genetically determined SRNS with calcineurin inhibitors. The economic model for population 2 reflected these findings. However, the survival benefit achieved by 2% of patients with genetically determined SRNS in the comparator arm caused the ICER for genetic testing in populations 2 and 3 to be more costly and less effective.

Table 20 Incremental cost-effectiveness ratio of genetic testing versus no testing – QALYs for populations 2 & 3

	Cost	Incremental cost	Effectiveness (QALYs)	Incremental effectiveness (QALYs)	ICER
Affected individuals (population 2)					
Index test and associated interventions	$352,277	$1,739	11.52	-0.00	-$360,828
Comparator	$350,538		11.53		
Affected individuals + cascade testing (populations 2 and 3)					
Index test and associated interventions	$379,058	$1,977	16.92	-0.01	-$285,999
Comparator	$377,082		16.92		

ICER = incremental cost-effectiveness ratio; QALYs = quality adjusted life years
Source: DCAR Table 15, as revised in the rejoinder.

The overall costs and outcomes, and incremental costs and outcomes (number of informed reproductive decisions) are shown in Table 21. When only reproductive decision making is considered, each genetic test of an affected individual plus associated cascade testing results in 1.08 informed reproductive decisions made by affected individuals and their first degree relatives. This translates to an ICER of $1,990 per informed reproductive decision.

Table 21 Incremental cost-effectiveness ratio of genetic testing versus no testing – informed reproductive decisions for populations 2 & 3

	Cost	Incremental cost	Effectiveness (informed reproductive decision)	Incremental effectiveness (informed reproductive decision)	ICER
Cost per informed reproductive decision made (populations 2 and 3)					
Index test and associated interventions	$395,961	$2,151	1.08	1.08	$1,990
Comparator	$393,810		0.00		

ICER = incremental cost-effectiveness ratio
Source: DCAR Table 16, as revised in the rejoinder.

Key drivers of the economic model for populations 2 and 3 are presented in Table 22.

Table 22 Key drivers of the economic model for populations 2 & 3

Description	Method/Value	Impact
No discounting of reproductive decisions	The model registered all reproductive decisions in the first model cycle, so no discounting is applied. Discounting future reproductive decisions would increase the ICER. The size of the impact is uncertain.	Uncertain, favours intervention
Uptake of kidney biopsy for SRNS	The model assumed 100% patients with SRNS in the 'NO TEST' scenario receive a kidney biopsy to establish a definitive diagnosis	Moderate, favours the intervention
Time horizon	The model applied an annual eGFR decline calculated for each sub-population based on limited trial evidence. The model extrapolated lifetime benefits for patients with aHUS who respond to eculizumab based on a 26-week trial.	Low, favours comparator

ICER = incremental cost effectiveness ratio; SRNS = steroid resistant nephrotic syndrome
Source: DCAR, Table 17

13. Financial/budgetary impacts

The DCAR used an epidemiological approach and prevalence rates of relevant kidney disease for each population to estimate the number of patients eligible for WGS.

For population 1, the financial implications to the MBS were estimated to be $1.61 million in 2021 and remaining approximately steady until 2025 due to capacity constraints (Table 23). The total financial implication to the MBS was estimated to be $7.91 million over five years.

Table 23 Estimated number of population 1 patients that are likely to receive WGS and the financial implications to the MBS, PBS, and the Government

Description	2021-2022	2022-2023	2023-2024	2024-2025	2025-2026
Number of patients likely to require WGS	789	723	796	715	805
Cost of WGS	$1,609,638	$1,474,730	$1,623,566	$1,459,215	$1,642,613
Cost of the reinterrogation test	$0	$0	$0	$0	$100,441
MBS-listed IVF services that are likely to be affected by listing the WGS	$0	$0	$0	$0	$0
Financial implications to the PBS	$0	$0	$0	$0	$0
Financial implications to the Government	$1,609,638	$1,474,730	$1,623,566	$1,459,215	$1,743,055

IVF = *in vitro* fertilisation; MBS = Medicare Benefits Schedule; PBS = Pharmaceutical Benefits Schedule; WGS = Whole genome sequencing
Source: DCAR Table 18, as revised in the rejoinder.

For population 2, the estimated total financial implication to the Government was $265,682 over five years (Table 24).

Table 24 Estimated number of population 2 patients that are likely to receive WGS and the financial implications to the MBS, PBS, and the Government

Description	2021-2022	2022-2023	2023-2024	2024-2025	2025-2026
Total number of patients likely to require WGS each year	27	25	28	25	28
Cost of WGS	$55,906	$51,246	$56,439	$50,644	$56,788
Cost of the reinterrogation test (with a negative WGS result)	$0	$0	$0	$0	$11,767
Other cost to the MBS	-$1,547	-$1,768	-$2,233	-$2,426	-$2,910
Financial implications to the PBS	-$833	-$1,596	-$2,437	-$3,191	-$4,037
Financial implications to the Government	$53,526	$47,882	$51,769	$45,027	$61,608

MBS = Medicare Benefits Schedule; PBS = Pharmaceutical Benefits Schedule; WGS = Whole genome sequencing
Source: DCAR Table 19 (unchanged in the rejoinder).

For population 3 (cascade testing), the estimated total financial implication to the Government was estimated to be $8.08 million over five years (Table 25).

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Table 25 Estimated number of population 3 individuals that are likely to receive cascade testing and the financial implications to the MBS, PBS, and the Government

Description	2021	2022	2023	2024	2025
Estimated number of cascade tests required	2,774	2,542	2,798	2,515	2,831
Cost of cascade testing	$943,236	$864,183	$951,401	$855,088	$962,544
Other cost to MBS-listed services	$722,133	$661,379	$727,940	$653,971	$736,031
Financial implications to PBS	$0	$0	$0	$0	$0
Financial implications to the Government	$1,665,369	$1,525,562	$1,679,341	$1,509,058	$1,698,574

MBS = Medicare Benefits Schedule; PBS = Pharmaceutical Benefits Schedule
Source: DCAR Table 20, as revised in the rejoinder.

The cost of reproductive partner testing was estimated to be approximately $600k per annum (Table 26).

Table 26 Estimated cost of reproductive partner testing

Description	2021	2022	2023	2024	2025
Number of cascade tests	2,774	2,542	2,798	2,515	2,831
Number of FDR probands detected via cascade testing (25% of those tested)	694	635	700	629	708
Number of probands detected via affected individual testing	587	538	592	532	599
Total number of probands detected	1281	1173	1292	1161	1307
Number of probands eventually having at least one child (41.46% of probands*)	531	487	536	481	542
Cost of reproductive partner testing	$637,231	$583,825	$642,748	$577,679	$650,272

FDR = first-degree relative
* = 41.46% of the all family households had at least one child, according to the Australian Institute of Family Studies (2018 data).
Source: Department's calculations, based on MSAC advice on the fee ($1200) and utilisation estimates from the rejoinder. Assumes all genetic variants have recessive mode of inheritance, and all reproductive partners will desire to be tested. Does not include costs to other MBS-listed services e.g. genetic counselling.

14. Key issues from ESC for MSAC

ESC key issue	ESC advice to MSAC
Quality of evidence	There was limited evidence beyond ascertaining a genetic diagnosis of affected individuals suggesting potential clinical utility, potential clinical effectiveness and potential improved safety. Among those patients assigned a genetic diagnosis, the proportion who also have prognostic or predictive utility was not established. There was high uncertainty as to whether this testing would translate into improved health outcomes for affected individuals.
Diagnostic yield and Clinical validity	There was no descriptive summary (average and range) of diagnostic yield (proportion of variant positive cases) across the entirety of the genes tested. There was no evidence on how well the genotype predicted phenotype.

ESC key issue	ESC advice to MSAC
Clinical utility and effectiveness	No direct evidence was provided on the effects on clinical management and health outcomes of affected individuals. Potential clinical utility was suggested by prognostic evidence in those with aHUS (where variant status was reported to be related to mortality in one study), and predictive validity evidence in affected individuals with ADPKD, SRNS and aHUS (where variant status was reported to predict a difference in the extent of benefit from treatment, noting that such treatment would already have been indicated). No evidence was presented to support a change in the course of disease following early genetic diagnosis in asymptomatic relatives of a proband.
Consistency with Alport syndrome listing	MSAC's consideration of Application 1449 (Genetic testing for Alport syndrome) may provide a guide on parallel issues arising in this application.
Key potential benefit not captured	The economic model currently does not account for any health benefit for affected individuals. If MSAC agrees that anecdotal benefits of CKD secondary prevention are plausible, they could be explored in a threshold analysis.
Discounting of consequences of future informed reproductive decisions	The current model assumes all reproductive decisions are made in the first model cycle. MSAC should consider whether reproductive decisions occurring in the future should be subject to discounting. The methodological consensus is that all costs and benefits should be discounted at the same rate according to their time of occurrence.
ICERs focused on lifetime costs of disease	The reported ICERs captured little by way of clinical benefit (other than diagnosis) and focused on lifetime cost implications. While these costs are direct and medical, they may not be relevant to the present decision-making. MSAC should consider in particular if lifetime disease costs are relevant when calculating the ICER per informed reproductive decision.
Financial implications	There was uncertainty around assumed input values. Costs of IVF were applied in the same year as genetic testing while in reality they may occur much later in time. Cost offsets from reduced ultrasound utilisation were calculated assuming perfect adherence to guidelines and may be overestimated. The financial estimates did not reflect all cost implications captured in the economic model due to appropriately different time horizons.
Policy considerations	ESC noted the following policy issues: WES versus WGS, technological change and its cost implications, demand for genetic services, wait times, geneticist and nephrologist conference, and mainstreaming of genetic testing.

ESC discussion

ESC noted this application was for the Medicare Benefits Schedule (MBS) listing of genetic testing for heritable kidney disease (other than Alport syndrome) in five populations:

- Population 1 (adults): Whole-genome sequencing (WGS) for germline gene variants in at least one gene causative for heritable cystic kidney disease

- Population 2 (children): WGS for germline gene variants in at least one gene causative for heritable chronic kidney disease in children (<18 years old)

- Population 3: Genetic testing in first-degree relatives of index cases for familial germline gene variants identified in genes causative for heritable kidney disease

- Population 4: Genetic testing for reproductive decision making (Department added)

- Population 5: Genetic testing for determining variant(s) in a fetus (Department added).

ESC accepted the point made via public consultation that the originally proposed term of "inherited" kidney disease may be inappropriate as some genetic kidney disease is caused by *de novo* variants, and advised that, consistent with MSAC-preferred terminology, the word "heritable" should be preferred, including in any MSAC-supported item descriptors.

ESC noted the support from the public consultation, suggesting that genomic testing could provide clinical utility of certainty in diagnosis and prognosis, assign a diagnosis for atypical disease presentation, predict a diagnosis of ADPKD before adulthood, shorten the diagnostic odyssey, provide earlier access to treatment dependent upon genotype, and lead to better clinical management, including reduced use of renal biopsy, negative genetic results from cascade testing with avoided monitoring, and informed family planning. Consumer feedback also noted by ESC included that funding this testing would improve equity of access, and that the value of knowing can be empowering.

ESC noted that population groupings in the DCAR differed from those in the PICO, but accepted them because the new groups were based on KidGen[37] advice. ESC expressed concern about the leakage of items AAAA1 and AAAA2 to other kidney diseases, but also conceded that there would be little reason to genetically test these other patients. ESC queried whether reproductive partner testing (item DDDD) should be restricted to the partners of probands whose variants are not known to have a dominant mode of inheritance.

ESC noted that, in the pre-ESC response, the applicant claimed that WGS should be used for ADPKD and whole exome sequencing (WES) for all other genetic testing. ESC agreed with the rejoinder that WGS is the preferred method of testing (as was the opinion of KidGen), as it is better at detecting the types of variants in question and is more efficient of pathology resources. Further, ESC noted that there are five sites in Australia accredited to perform WGS and 15 sites that can perform next generation sequencing (NGS). ESC considered that, aside from specifying WGS for the two affected individuals items, the item descriptors could be technology agnostic. The pre-ESC response also highlighted that the populations assessed are dichotomised by age, but that the presentations of many of the variants are not age-specific.

ESC noted that the DCAR did not present any data on comparative safety. The claims that it is "possible for harm to be caused by genetic testing through genetic misdiagnosis (or overdiagnosis), missed diagnosis, or incidental findings" and "harm can also be caused by no genetic testing through adverse events associated with inappropriate therapeutic

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[37] KidGen is an Australian collaboration between clinical, diagnostic and research teams, with the aim of better understanding the causes of heritable kidney disease. For more information, see http://www.kidgen.org.au/.

interventions" were not supported by any evidence so there was no objective basis to judge their reasonableness.

ESC noted that the DCAR used a linked evidence approach to analyse clinical trial data for populations 1–3. ESC noted the lack of high-quality evidence to support the clinical claims of superior safety and effectiveness in terms of disease diagnosis and change in clinical management of patients, and noted that any evidence presented in the DCAR had a high risk of bias.

ESC noted that the composite diagnostic yield varied by population; being higher for population 1 (79%) and ranging from 17% to 29% within population 2. ESC acknowledged that the stepwise approach used was to firstly demonstrate diagnostic yield for each indication, which were all >10% and therefore are considered above an acceptable threshold set previously in CUC-based applications. The diagnostic yield analysis of selected exemplars may have consequences for familial testing. A descriptive summary (average and range) of diagnostic yield was not provided.

ESC noted that in population 2 (glomerular diseases subpopulation), six studies found that immunosuppressive therapies failed to prevent the progression to ESKD in patients with genetically determined SRNS. Genetic diagnosis could potentially prevent ineffective treatment being trialled, but ESC considered there to be no direct evidence that genetic diagnosis changes management. In population 2 (complement diseases subpopulation), one retrospective study found that the death rate was higher in aHUS patients with genetic variants compared with those without genetic variants. ESC disagreed with how this evidence was presented in the assessment report, and reclassified the "clinical utility" as "prognosis", as the evidence for change in management was in the form of prognostic evidence rather than direct evidence that diagnosis changed clinical management.

ESC also reclassified "clinical utility" evidence relating to treatment effect modification by genetic variant status as "predictive validity", because the evidence for health benefit from change in management was in the form of clinical prediction of therapeutic effectiveness by genetic test result. ESC considered its reclassification to be more accurate because there was no direct evidence that the test result changed the clinical management.

ESC noted the small number of studies that reviewed gene variant status and its relationship to determining suitability of transplant compatibility. However, the genetic test used in these studies was Sanger sequencing (not WGS) and ESC considered the claims for a role for genetic testing in this to be unsubstantiated. ESC also noted the preimplantation genetic testing (PGT) studies using Sanger sequencing to detect variants in the polycystic kidney disease 1 (*PKD1*) and polycystic kidney disease 2 (*PKD2*) genes; however, again, WGS was not used and ESC considered the evidence to be limited. ESC also noted the limited evidence available to support the claim that genetic testing influences reproductive choices for population 2.

ESC noted the comprehensive modelling of kidney disease progression used in the economic analysis. ESC considered that the complexity of the modelling (including the number of inputs, health states, a long time horizon, and multiple sources of evidence) made it somewhat difficult to examine model performance beyond its face validity. ESC highlighted that model validation presented in the DCAR did not provide a conclusive assessment of model robustness. ESC considered that further validation may increase MSAC's willingness to accept the results of the economic evaluation.

ESC recalled that, in the context of MSAC application 1573, MSAC had preferred the outcome "informed reproductive decisions" as the denominator for incremental cost-effectiveness ratios (ICERs) where reproductive decisions were affected and quality adjusted life years (QALYs) could not be generated, since MSAC seeks to optimise informed reproductive decision making. ESC also considered that ICERs per QALY are preferred if they can be supported, and noted that, for 1573 MSAC accepted all types of reproductive decisions included in the model, as well as their modelled cost consequences. However, ESC advised that all costs and consequences of the outcomes "informed reproductive decisions" or QALYs should be subject to discounting according to when they occur in time, given an anticipated delay between the information becoming available and the information being acted upon. Consequently, ESC considered that the approach taken in the evaluation, assuming that all reproductive decisions occur in the first model cycle, may not be appropriate.

ESC noted that the economic evaluation resulted in high costs in both the intervention and comparator arms, and a relatively small incremental cost. Considering also nil incremental health benefits of testing, ESC queried whether the approach to economic evaluation was appropriate, and in particular if all costs modelled were relevant to the present MSAC decision. ESC noted that the negative incremental QALYs reported by the economic evaluation for populations 2 and 3 were due to forgoing calcineurin inhibitor treatment in patients with evidence of a monogenic form of SRNS, due to its low chances of success in this population (2% achieving complete response, compared to 32% in non-genetic SRNS). Because no other health outcome was modelled, the small loss of QALYs associated with forgoing this treatment could not be offset, and resulted in a modelled estimate of negative incremental health outcomes from genetic testing. ESC considered this estimate to be based on a minor and incidental finding, and advised that the proposed intervention should not be assessed exclusively on the negative incremental health outcomes reported from the economic model. Rather, the potential health gains of genetic testing not currently modelled should also be taken into consideration.

ESC noted that there was no evidence of any other health gains to justify the cost of testing. ESC acknowledged that aspects of the "value of knowing" have been argued to be relevant to this application, but there is no QALY value associated with this. ESC also noted the claimed additional health gains of secondary prevention (such as monitoring, lifestyle changes, and use of ACE inhibitors), but these were not supported by evidence and were not modelled. ESC also considered that improved patient management following genetic testing could lead to reductions in preventable all-cause hospitalisations, particularly in the context of kidney disease comorbidity with cardiovascular disease, hypertension and diabetes – but again, in the absence of evidence, these potential benefits (both health gains and cost offsets) were not modelled. ESC noted that similar concerns regarding modelled benefits were considered for application 1449 (Alport syndrome), but recalled that this previous model did not account for the reductions in renal biopsies even though this benefit was accepted by MSAC.

ESC noted that the ICERs per informed reproductive decision were $3,351 for populations 1 & 3, and $1,990 for populations 2 & 3, but noted that limitations of the data supporting this claim include:

- rate of pre-implementation/prenatal diagnosis in Victoria from 1977 to 2016[38] and whether it is nationally representative
- applicability of evidence of reproductive decisions made by 48 Australian couples following the diagnosis of their children with monogenic disorders[39], to kidney disease specifically
- applicability of UK patients' attitudes toward pre-implantation genetic diagnosis and prenatal diagnosis with ADPKD[40] to Australia.

ESC noted the uncertainty associated with the modelling, some of which may favour the intervention: the costs of ADPKD in first-degree relatives, and the uptake of kidney biopsy for SRNS. Moreover, ESC considered that the key drivers of the economic model identified by the DCAR were likely affected by the fact that no benefits were modelled, and consequently were of limited use in informing MSAC's decision.

ESC noted that eligibility and uptake of testing were key drivers for the financial impact for population 1, but considered that these numbers were uncertain. ESC noted that the estimated cost of population 1 was roughly double that for Alport syndrome and the estimated cost of population 2 was much smaller. For population 3, ESC noted that most of the "other costs to the MBS" were for *in vitro* fertilisation (IVF), with 10% ultrasound offset. As a consequence of informed reproductive decision making, ESC queried whether this cost of IVF was relevant in the same year as the related genomic test or if it would be delayed. ESC considered the cost offsets associated with reductions in ultrasound screening to be potentially overestimated, because they were calculated under the assumption of perfect adherence to clinical guidelines.

15.   Other significant factors

Nil.

16.   Applicant comments on MSAC's Public Summary Document

The applicant had no comment.

17.   Further information on MSAC

MSAC Terms of Reference and other information are available on the MSAC Website:
[visit the MSAC website](#)

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[38] Poulton A, et al. 2018, 'Prenatal and preimplantation genetic diagnosis for single gene disorders: A population-based study from 1977 to 2016', *Prenat Diagn*, 38(12): 904-10.
[39] Stark Z, et al. 2019, 'Does genomic sequencing early in the diagnostic trajectory make a difference? A follow-up study of clinical outcomes and cost-effectiveness', *Genet Med*, 21(1): 173-80.
[40] Swift O, et al. 2016, 'Attitudes in Patients with Autosomal Dominant Polycystic Kidney Disease Toward Prenatal Diagnosis and Preimplantation Genetic Diagnosis', *Genet Test Mol Biomarkers*, 20(12): 741-6.